



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/068,238	02/05/2002	Constance A. Bell	07039-372001	7696
26191	7590	01/30/2004	EXAMINER	
FISH & RICHARDSON P.C. 3300 DAIN RAUSCHER PLAZA 60 SOUTH SIXTH STREET MINNEAPOLIS, MN 55402			STRZELECKA, TERESA E	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/068,238

Applicant(s)

BELL ET AL.

Examiner

Teresa E Strzelecka

Art Unit

1637

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed, after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-56 is/are pending in the application.
- 4a) Of the above claim(s) 1-31 and 48-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11062002. 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II (claims 32-47) in Paper No. 24112003 is acknowledged.
2. Claims 1-31 and 48-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 24112003.
3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on June 11, 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The hyperlinks are on page 22, line 31 and page 26, line 6.

Appropriate correction is required.

Art Unit: 1637

6. The disclosure is objected to because of the following informalities: Table 1 contains sequences of primers, which are not identified by SEQ ID NOs.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 32, 35-38, 41-43, 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID NO: 1-16. Thus, applicant has express possession of only sixteen

Art Unit: 1637

particular primers and probes for the capB, pagA and lef genes of Bacillus anthracis, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

"A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the primer or probe for a capB gene, for example, lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the for specific primers and probes, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a pair of capB primers", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

"...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely by its functional utility, as a primer or probe, without any definition of the particular probes or primers claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise SEQ ID NO: 1-16. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim interpretation

9. In claims 32-47, the terms "primers" and "probes" are interpreted as oligonucleotides hybridizable to a target nucleic acid. Further, as there is no restriction that the primers have to be different from the probes, they are considered to be the same, unless their sequences are different.

10. In claims 36, 42 and 47, the limitation of a package insert having instructions for using primers and probes is not taken into account when comparing claims with the prior art, since the instructions (printed matter) do not constitute a structural limitation on primers or probes.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 32, 36-38, 42, 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001).

A) Regarding claims 32 and 36, Ramisse et al. teach two oligonucleotides which are primers for the capB gene of B. anthracis (Table 2, Fig. 1).

Regarding claims 37, 38 and 42, Ramisse et al. teach four oligonucleotides which are primers for the pagA gene of B. anthracis (Table 2, Fig. 1).

Regarding claims 43 and 47, Ramisse et al. teach four oligonucleotides which are primers for the lef gene of B. anthracis (Table 2, Fig. 1).

B) Ramisse et al. do not teach donor or acceptor fluorescent moieties or probes labeled with donor or acceptor fluorescent moieties.

C) Regarding claims 32, 38 and 43, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

D) Regarding claims 32, 38 and 43, Qi et al. teach real-time PCR detection of *B. anthracis* using two primers and two probes with sequences complementary to the *rpoB* gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the *B. anthracis* detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

“Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses.” (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of *B. anthracis*, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and “The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive

when extracted DNA is used as a template for PCR. ... The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples.” (page 3726, last paragraph; page 3727, first paragraph).

14. Claims 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001) as applied to claim 32 above, and further in view of Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) Regarding claims 33-35, Ramisse et al. teach primers for detection of capB gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-4.

Regarding claims 32 and 35, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 32 and 35, Qi et al. teach real-time PCR detection of *B. anthracis* using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et

al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al., Wittwer et al. and Qi et al. with the use of functionally equivalent primers selected from the sequence of Makino et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Makino et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different

primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

15. Claims 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001) as applied to claim 38 above, and further in view of Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) Regarding claims 39-41, Ramisse et al. teach primers for detection of pagA gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 5-8.

Regarding claims 38 and 41, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 38 and 41, Qi et al. teach real-time PCR detection of *B. anthracis* using two primers and two probes with sequences complementary to the *rpoB* gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

B) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the *pagA* gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the *pagA* gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the *pagA* gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the *pagA* gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the *pagA* gene (Table 2). Further, Price et al. teach primers for amplification of *pagA* gene (Table 1), which were designed from published *pag* sequence (page 2358, sixth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al., Wittwer et al. and Qi et al. with the use of functionally equivalent primers selected from the sequence of Price et al., since Ramisse et al. expressly teach primer selection using commercially available software for *B. anthracis* detection from the *B. anthracis* published sequences and since Price et al. provide such published sequences for the software program to analyze, and also teach primers for amplification of *pagA*.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a

specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

16. Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001) as applied to claim 43 above, and further in view of Bragg et al. (Gene, vol. 81, pp. 45-54, 1989) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) Regarding claims 44-46, Ramisse et al. teach primers for detection of *lef* gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 9-12.

Regarding claims 43 and 46, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 43 and 46, Qi et al. teach real-time PCR detection of *B. anthracis* using two primers and two probes with sequences complementary to the *rpoB* gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

B) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the *lef* gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the *lef* gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the *lef* gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the *lef* gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the *lef* gene (Table 2). Further, Bragg et al. teach primers for sequencing of *lef* gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al., Wittwer et al. and Qi et al. with the use of functionally equivalent primers selected from the sequence of Bragg et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Bragg et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY

SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

17. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


**JEFFREY FREDMAN
PRIMARY EXAMINER**

Ts
January 26, 2004